PA NT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
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CP2/5C24
Arlington, VA 22202
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in its capacity as elected Office

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International filing date (day/month/year) 06 June 2000 (06.06.00)	**Priority date** (day/month/year) 09 June 1999 (09.06.99)
Applicant BARTHOLEYNS, Jacques et al	

1. *The designated Office is hereby notified of its election made:*

[X] in the demand filed with the International Preliminary Examining Authority on:

05 December 2000 (05.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

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made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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(54) Title: NEW MOLECULAR COMPLEXES PRESENTING HIGH AFFINITY BINDING WITH RESPECT TO MONOCYTE DERIVED CELLS AND THEIR USES IN THERAPY

(57) Abstract: The invention concerns a molecular complex between a tissue extract containing at least one known component and unknown components and a molecular vector comprising a particle bearing sugars and/or polypeptides, said molecular vector being able to recognize: said known component of said tissue extract, and a phagocytic receptor of monocyte derived cells, with the proviso that said polypeptides are different from antibodies.

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/EP 00/05202

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/12 A61K35/74 A61K35/76 A61K35/14 A61K39/00
C12N5/06 C12N5/08 A61P35/00 A61P31/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 17084 A (J.R. KALDEN ET AL.) 15 May 1997 (1997-05-15) page 8, line 9 - line 22; claims 1,2,6,12; examples 1,2 ---	1-16
A	WO 98 13378 A (RIJKSUNIVERSITEIT TE LEIDEN) 2 April 1998 (1998-04-02) claims ---	1-16
A	WO 97 01760 A (UNIVERSITE PIERRE ET MARIE CURIE) 16 January 1997 (1997-01-16) claims ---	1-16
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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11 December 2000	18/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Ryckebosch, A

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	A. MABONDZO ET AL.: "ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY AND NEUTRALIZATION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 BY HIGH AFFINITY CROSS-LINKING OF gp41 TO HUMAN MACROPHAGE Fc IgG RECEPTOR USING BISPECIFIC ANTIBODY" JOURNAL OF GENERAL VIROLOGY, vol. 75, 1994, pages 1451-1456, XP002132667 page 1454, right-hand column, paragraph 2 -page 1455, left-hand column, paragraph 3 -----	1-16

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr nal Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9717084 A	15-05-1997	DE 19541284 A	30-05-1996
		CA 2236888 A	15-05-1997
		EP 0859628 A	26-08-1998
		JP 2000500124 T	11-01-2000
WO 9813378 A	02-04-1998	EP 0849275 A	24-06-1998
		AU 4401997 A	17-04-1998
WO 9701760 A	16-01-1997	FR 2736197 A	03-01-1997
		EP 0847528 A	17-06-1998

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(57) Abstract: The invention concerns a molecular complex between a tissue extract containing at least one known component and unknown components and a molecular vector comprising a particle bearing sugars and/or polypeptides, said molecular vector being able to recognize: said known component of said tissue extract, and a phagocytic receptor of monocyte derived cells, with the proviso that said polypeptides are different from antibodies.

NEW MOLECULAR COMPLEXES PRESENTING HIGH AFFINITY BINDING WITH RESPECT TO MONOCYTE DERIVED CELLS AND THEIR USES IN THERAPY

The invention relates to new molecular complexes presenting high affinity binding with respect to monocyte derived cells and their uses in therapy.

Blood monocytes in physiological conditions leave the blood stream flow to reach tissues where they differentiate into resident macrophages (for example: lung macrophages, kupffer cells in liver, skin macrophages, osteoclasts in bone, microglial cells in brain ...), or into professional antigen presenting cells (for example : dendritic cells in peripheral tissues or lymphnodes, Langerhans cells in skin ...).

Differentiation of blood monocytes can also be achieved *ex vivo* under defined culture conditions (see applications WO94/26875, WO96/22781, WO97/44441, WO99/13054); however, the macrophages or the dendritic cells obtained in culture do not achieve tissue specificity similar to the one obtained *in vivo*).

Furthermore, the induction of an immune response has been documented when the antigens are known. However, regarding the induction of an immune response towards unknown antigens (particularly tumor antigens), a targeting of these antigens to specific receptors of the antigen presenting cells is required ; this is an objective of the present invention.

One of the aims of the invention is to provide monocyte derived cells which have acquired a tissue specificity.

Another aim of the invention is to provide an *ex vivo* method for stimulating cellular and/or humoral immune responses against unknown components of a tumor tissue extract.

Another aim of the invention is to provide *in vivo* specific cellular and/or humoral immune responses against unknown component of tumor tissue extract.

All these aims are achieved through the invention, which gives access to new molecular complexes having high affinity with tissue extracts on the one hand, and high affinity with monocyte derived cells on the other hand.

More precisely, the invention relates to a molecular complex between a tissue extract containing at least one known component and unknown components and a molecular vector comprising a particle bearing polypeptides and/or sugars, said molecular vector being able to recognize :

- said known component of said tissue extract, and
- a phagocytic receptor of monocyte derived cells,

with the proviso that polypeptides are different from antibodies.

The expression "*known component*" means identified tissue antigens, polypeptides or oligosaccharides or an hapten expressed or transfected on the cell membrane of tissues or tumors.

The expression "*unknown component*" means "complex mixture of proteins and saccharides present in cellular extracts of tumors or tissues (lysates, apoptotic extracts,...)

The expression "*molecular vector*" corresponds to a carrier of molecular structure.

The expression "*recognize said known component of said tissue extract*" means that it presents a high affinity and/or avidity ($>10^{-6}$ M) for said component.

The expression "*recognize a phagocytic receptor of monocyte derived cells*" means that it is a ligand for such receptor.

The expression "*polypeptides are different from antibodies*" means that they are not monoclonal or polyclonal antibodies with Fc and Fab parts.

A phagocytic receptor of monocyte derived cells is a receptor such that, when interacting with a ligand, in this case, the molecular complex, it initiates uptake of said ligand.

The phagocytic status means that the monocyte derived cells have gained, after a few days of culture, for instance, about 4 to about 10 days, a high

phagocytic activity. (This phagocytic activity can be visualized and quantified by measuring, for instance under the microscope, the uptake of yeast particles).

The expression "*monocyte derived cells (or MDCs)*" designates macrophages or dendritic cells derived from blood monocytes.

According to an advantageous embodiment, the invention relates to a molecular complex wherein the molecular vector comprises a particle bearing polypeptides and/or sugars such that :

- at least one of the said polypeptides and/or sugars recognizes said known surface component of the tissue extract,
- at least one of the said sugars and/or polypeptides recognizes phagocytic receptors of monocyte derived cells such as receptors for mannose or for oligosaccharides or Fc receptors of monocyte derived cells.

There are thus four different possibilities :

1) at least one of the said polypeptides of the particle can recognize a known component of the tissue extract and at least one of the said polypeptides of the particle can recognize a phagocytic receptor of monocyte derived cells,

2) at least one of the said polypeptides of the particle can recognize a known component of the tissue extract and at least one of the said sugars of the particle can recognize a phagocytic receptor of monocyte derived cells,

3) at least one of the said sugars can recognize a known component of the tissue extract and at least one of the said sugars of the particle can recognize a phagocytic receptor of monocyte derived cells,

4) at least one of the said sugars can recognize a known component of the tissue extract and at least one of the said polypeptides of the particle can recognize a phagocytic receptor of monocyte derived cells.

The nature of the bond between the sugar and the known component is formed of hydrogen, Vanderwaals, hydrophobic interactions and salt bridges.

The nature of the bond between the sugar and the monocyte derived cells is mainly hydrogen, Vanderwaals, hydrophobic interactions and salt bridges.

The nature of the bond between the polypeptides and the known component is mainly hydrogen, Vanderwaals, hydrophobic interactions and salt bridges.

The nature of the bond between the polypeptide and monocyte derived cells is mainly hydrogen, Vanderwaals, hydrophobic interactions and salt bridges.

In an advantageous embodiment of the molecular complex of the invention, the molecular vector comprises or is a particle of about 0,1 to about 2 μm of biocompatible polymer comprising :

- surface polypeptides and/or sugars, preferably covalently linked to the surface of said particle, with said surface polypeptides and/or sugars recognizing said known component of the tissue extract, and
- mannosylated residues recognizing the mannose or oligosaccharide receptors of monocyte derived cells.

According to an advantageous embodiment, in the molecular complex of the invention, the tissue extract comprises macroscopic fragments or killed or irradiated or haptenised human or animal tumor cells such as lysates or apoptotic bodies, or killed pathogens, such as viruses or bacteria.

According to an advantageous embodiment, in the molecular complex of the invention, the polypeptide of the particle recognises one known epitope of the tissue extract chosen among known tumor antigens such as (tumor peptide antigen) MelanA/MART-1, MAGE, BAGE, GAGE families, MUC, EGF-R, ERB-2, PSA, PSMA, HSP70, CEA, P53, RAS, Tyrosinase, gp100,....

According to another advantageous embodiment, in the molecular complex of the invention, the tissue extract comprises normal tissue parts such as tissue membranes, tissue factors, tissue proteins, macroscopic fragments of tissue such as lysates or apoptopic bodies, said tissue being originating from any part of human or animal body or cellular extracts thereof, in particular from thymus, lung, pancreas, cartilage, endothelium, neuromuscular junctions,

prostate, sexual organs, bladder, muscles, peripheral nerves, CNS extracts, spleen, liver, bone, heart, skin cells.

In the molecular complex of the invention, the polypeptide and/or sugars of said particle form(s) high affinity binding with any component of said tissue extract.

In the molecular complex of the invention, the polypeptide and/or sugars of the particle form(s) high affinity binding with a phagocytic receptor of a monocyte derived cell.

The expression "*high affinity binding*" means that the affinity constant Ka is equal to or higher than 10^6 M or the equilibrium dissociation constant K_D is equal to or lower than 10^{-6} M.

According to an advantageous embodiment, the monocyte derived cells recognized by the molecular complex of the invention are macrophages, dendritic cells, or antigen presenting cells.

The invention also relates to monocyte derived cells such as prepared according to a process comprising the step of contacting monocyte derived cells with a molecular complex according to the invention.

The invention also relates to monocyte derived cells such as prepared according to a process comprising contacting monocyte derived cells with a molecular complex according to the invention, under conditions enabling phagocytosis of said molecular complex by said monocyte derived cells, intracellular degradation and processing of the known and unknown components of the tumor tissue extract and the presentation of said known and unknown components on the peripheral membrane of the monocyte derived cells together with MHC 1 and MHC II molecules.

The monocyte derived cells are immature dendritic cells for the phagocytosis, which then mature for the induction of immune response.

The invention also relates to monocyte derived cells such as prepared according to a process comprising contacting monocyte derived cells with a

molecular complex as described above, under conditions enabling phagocytosis of such molecular complex by the monocyte derived cells.

The monocyte derived cells are non-activated macrophages (4/8 days of culture).

The invention also relates to an *ex vivo* method for stimulating cellular and/or humoral immune responses against unknown components of a tumor tissue extract comprising contacting monocyte derived cells with a molecular complex according to the invention, under conditions enabling phagocytosis of said molecular complex by monocyte derived cells, intracellular degradation and processing of the known and of unknown components of the tumor tissue extract and the presentation of said known and unknown components on the peripheral membrane of the monocyte derived cells, together with MHC I and II molecules.

The invention also relates to a method of inducing *in vivo* specific cellular and/or humoral immune responses against unknown components of tumor tissue extract comprising injections of a molecular complex according to the invention, for instance by intramuscular, subcutaneous, local or intravenous route.

According to an advantageous embodiment, said method of inducing *in vivo* specific cellular and/or humoral responses against unknown components of a tumor tissue extract, comprises sequential and/or simultaneous injections of monocyte derived cells presenting known and unknown components of said tumor tissue extract, together with MHC I and II molecules, as defined above, and of molecular complexes as described above.

The invention also relates to a method for conditioning *ex vivo* monocytes derived cells, and preferentially macrophages, for them to acquire tissue specificity, comprising contacting monocyte derived cells with a molecular complex according to the invention, under conditions enabling phagocytosis of said molecular complex by the monocyte derived cells.

The expression "*conditioning ex vivo human monocyte derived cells*" means that after phagocytosis of specific tissue extracts, the MDCs acquire characteristics of the corresponding tissue macrophages.

The expression "*acquire tissue specificity*" means that when the MDCs are injected *in vivo*, they will (concentrate) accumulate preferentially in the corresponding tissue.

The invention also relates to a method of treatment of diseases involving accumulation of conditioned monocyte derived cells as described above in specific tissue to induce tissue repair and/or regeneration comprising :

- either simultaneous and/or sequential injections of monocyte derived cells and of a molecular complex according to the invention, under conditions enabling phagocytosis,

- or injection of the monocyte derived cells which have previously phagocytosed a molecular complex according to the invention.

The expression "*accumulation of conditioned monocyte derived cells*" in a tissue means that, after systemic injection, at least 10% of the cells injected accumulate in the tissue within 24 h.

In the invention, the monocyte derived cells which are advantageously involved are human monocyte derived cells.

By way of example, the diseases which can be treated by the method of the invention are tissue/organ destruction or degenerative diseases, when tissue repair is required (skin, bone, nerve, neuromuscular regeneration).

The invention also relates to pharmaceutical compositions comprising, as active substance, monocyte derived cells which have been contacted with a molecular complex according to the invention, under conditions enabling phagocytosis of said molecular complex by monocyte derived cells, intracellular degradation and processing of the known and of unknown components of the tumor tissue extract and the presentation of said known and unknown components on the peripheral membrane of the monocyte derived cells, together with MHC I and II molecules.

The invention also relates to pharmaceutical compositions comprising, as active substance, monocyte derived cells, and preferentially macrophages, which have been contacted with a molecular complex according to the invention, under conditions enabling phargocytosis of said molecular complex by the monocyte derived cells.

EXAMPLE 1 : Application to a human melanoma tumor:

Apoptotic bodies are generated from a human melanoma cell line M17 by UV irradiation. They are added in basic medium to microparticles of 0.2 to 2 μm with covalently linked annexin V polypeptides and mannosyl residues. Annexin V presents a high affinity for phosphatidyl serine residues expressed on apoptodic bodies.

The microparticles contain a magnetic core and the molecular complexes (tumor apoptotic bodies - microparticles) are isolated on magnets. A working bank of molecular melanoma complexes is constituted and kept frozen.

Patients with metastatic melanoma are injected into 4 subcutaneous sites, one intradermal site plus one intravenous site with the defrost preparation.

The injections are repeated after 2 weeks and again one month later. Interaction with dendritic cells is occurring locally in the patient.

The induction of a specific immune response against the melanoma tumor is documented by humoral and cellular T responses against the known MAGE and MelanA/MART antigens expressed by the M17 cell line. The global antitumoral effect is shown by shrinkage (> 50%) of subcutaneous metastases, this response requires immune activation against multiple melanoma tumor antigens or than the targeted antigen.

EXAMPLE 2 : Application to tissue repair in a murine model:

Microparticles of 0.2 to 2 μm size presenting at their surface mannosyl residues are added to a suspension of killed murine hepatocytes, and molecular complexes are formed.

Macrophages are obtained by differentiation of murine bone marrow cells in culture and labelled with indium or an emittor of positons (example: Fluor 18).

These macrophages are grown for 16 h in the presence (a) or the absence (b) of molecular complexes.

Two millions of these macrophages are injected intravenously to the mice. After 2 hours, the biodistribution of the macrophages in the animal tissues is measured by gamma counting or PET-scan (SMV International). In case (a), 90% of the macrophages injected are in the liver while in case (b), only 20% of the macrophages are in liver. This indicates that the macrophages grown in the presence of the molecular complexes have gained a liver tissue specificity. If necrosis of the liver is previously induced, a fast regeneration is seen a few days after macrophage injection.

CLAIMS

1. Molecular complex between a tissue extract containing at least one known component and unknown components and a molecular vector comprising a particle bearing sugars and/or polypeptides, said molecular vector being able to recognize :

- said known component of said tissue extract, and
- a phagocytic receptor of monocyte derived cells,

with the proviso that said polypeptides are different from antibodies.

2. Molecular complex according to claim 1, wherein the molecular vector comprises a particle bearing polypeptides and/or sugars such that :

- at least one of the said polypeptides and/or sugars recognizes said known surface component of the tissue extract,
- at least one of the said sugars and/or polypeptides recognizes phagocytic receptors of monocyte derived cells such as receptors for mannose or for oligosaccharides or Fc receptors of monocyte derived cells.

3. Molecular complex according to claim 2, wherein the molecular vector comprises or is a particle of about 0,1 to about 2 μm of biocompatible polymer comprising

- surface polypeptides and/or sugars, preferably covalently linked to the surface of said particle, with said surface polypeptides and/or sugars recognizing said known component of the tissue extract, and
- mannolysated residues recognizing the mannose or oligosaccharide receptors of monocyte derived cells.

4. Molecular complex according to anyone of claims 1 to 3, wherein the tissue extract comprises macroscopic fragments or killed or irradiated or

haptenized human or animal tumor cells such as lysates or apoptotic bodies, or killed pathogens, such as viruses or bacteria.

5. Molecular complex according to claim 4, wherein the polypeptide of the particle recognises one known epitope of the tissue extract chosen among known tumor antigens such as (tumor peptide antigen) MelanA/MART-1, MAGE, BAGE, GAGE families ; MUC, EGF-R, ERB-2, PSA, PSMA, HSP70, CEA, P53, RAS, Tyrosinase, gp100,...

6. Molecular complex according to anyone of claims 1 to 3, wherein the tissue extract comprises normal tissue parts such as tissue membranes, tissue factors, tissue proteins, macroscopic fragments of tissue such as lysates or apoptopic bodies, said tissue being originating from any part of human **or** animal body or cellular extracts thereof, in particular from thymus, lung, pancreas, cartilage, endothelium, neuromuscular junctions, prostate, sexual organs, bladder, muscles, peripheral nerves, CNS extracts, spleen, liver, bone, heart, skin cells.

7. Molecular complex according to claim 6, wherein the polypeptide and/or sugars of said particle forms high affinity binding with any component of said tissue extract.

8. Molecular complex according to anyone of claims 1 to 7, wherein the monocyte derived cells recognized by said molecular complex are macrophages, dendritic cells, or antigen presenting cells.

9. Monocyte derived cells such as prepared according to a process comprising the step of contacting monocyte derived cells with a molecular complex according to anyone of claims 1 to 8.

10. Monocyte derived cells such as prepared according to a process comprising contacting monocyte derived cells with a molecular complex according to anyone of claims 1 to 5, under conditions enabling phagocytosis of said molecular complex by said monocyte derived cells, intracellular degradation and processing of the known and unknown components of the tumor tissue extract and the presentation of said known and unknown components on the peripheral membrane of the monocyte derived cells together with MHC I and MHC II molecules.

11. Monocyte derived cells such as prepared according to a process comprising contacting monocyte derived cells with a molecular complex according to any one of claims 1 to 3, 6 and 7, under conditions enabling phagocytosis of such molecular complex by the monocyte derived cells.

12. *Ex vivo* method for stimulating cellular and/or humoral immune responses against unknown components of a tumor tissue extract comprising contacting monocyte derived cells with a molecular complex according to anyone of claims 1 to 5, under conditions enabling phagocytosis of said molecular complex by monocyte derived cells, intracellular degradation and processing of the known and of unknown components of the tumor tissue extract and the presentation of said known and unknown components on the peripheral membrane of the monocyte derived cells, together with MHC I and II molecules.

13. Method of inducing *in vivo* specific cellular and/or humoral immune responses against unknown components of tumor tissue extract comprising injections of a molecular complex according to anyone of claims 1 to 5, for instance by intramuscular, subcutaneous, local or intravenous route.

14. Method of inducing *in vivo* specific cellular and/or humoral responses against unknown components of a tumor tissue extract, comprising sequential and/or simultaneous injections of monocyte derived cells presenting known and unknown components of said tumor tissue extract, together with MHC I and II molecules, as defined in claim 12, and of molecular complexes according to anyone of claims 1 to 5.

15. Method for conditioning *ex vivo* human monocytes derived cells, and preferentially macrophages, for them to acquire tissue specificity, comprising contacting monocyte derived cells with a molecular complex according to anyone of claims 1 to 3, or 6 and 7, under conditions enabling phagocytosis of such molecular complex by the monocyte derived cells.

16. Method of treatment of diseases involving accumulation of conditioned monocyte derived cells according to claim 15 in specific tissue to induce tissue repair and/or regeneration comprising :

- either simultaneous and/or sequential injections of monocyte derived cells and of a molecular complex according to anyone of claims 1 to 3, or 6 and 7, under conditions enabling phagocytosis,
- or injection of the monocyte derived cells which have previously phagocytosed a molecular complex according to anyone of claims 1 to 3 or 6 and 7.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WOB 99 AL IDM TARG		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05202	06/06/2000	09/06/1999
International Patent Classification (IPC) or national classification and IPC A61K35/12		
Applicant I.D.M. IMMUNO-DESIGNED MOLECULES et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/12/2000	13.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Deck, A Telephone No. +49 89 2399 8432

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05202

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-9 as originally filed

Claims, No.:

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 13, 14, 16.

because:

   ☒ the said international application, or the said claims Nos. 13, 14, 16 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	see separate sheet

No: Claims

2. Citations and explanations
see separate sheet

Concerning section III:

Claims 13, 14 and 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Concerning section V:

The invention relates to a complex between a tissue extract and a vector, said vector specifically recognizing the tissue and a phagocytic receptor on monocytes.
The invention further relates to monocytes contacted with said complex, methods for inducing tissue-specific immune responses and for treating diseases.

The available prior art documents neither disclose nor suggest the present invention which therefore meets the requirements of Article 33(2) and (3) PCT.

For the assessment of the present claims 13, 14 and 16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WOB 99 AL IDM TARG		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05202	06/06/2000	09/06/1999
International Patent Classification (IPC) or national classification and IPC A61K35/12		
Applicant I.D.M. IMMUNO-DESIGNED MOLECULES et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

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Date of submission of the demand	Date of completion of this report
05/12/2000	13.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Deck, A Telephone No. +49 89 2399 8432

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05202

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1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
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Claims, No.:

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- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
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- ☐ the description, pages:
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☐ the entire international application.

☒ claims Nos. 13, 14, 16.

because:

☒ the said international application, or the said claims Nos. 13, 14, 16 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

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☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	see separate sheet

No: Claims

2. Citations and explanations
see separate sheet

Conc rning section III:

Claims 13, 14 and 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted]00/05202

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/12 A61K35/74 A61K35/76 A61K35/14 A61K39/00
C12N5/06 C12N5/08 A61P35/00 A61P31/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 17084 A (J.R. KALDEN ET AL.) 15 May 1997 (1997-05-15) page 8, line 9 - line 22; claims 1,2,6,12; examples 1,2	1-16
A	WO 98 13378 A (RIJKSUNIVERSITEIT TE LEIDEN) 2 April 1998 (1998-04-02) claims	1-16
A	WO 97 01760 A (UNIVERSITE PIERRE ET MARIE CURIE) 16 January 1997 (1997-01-16) claims	1-16

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 December 2000	18/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ryckebosch, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. MABONDZO ET AL.: "ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY AND NEUTRALIZATION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 BY HIGH AFFINITY CROSS-LINKING OF gp41 TO HUMAN MACROPHAGE Fc IgG RECEPTOR USING BISPECIFIC ANTIBODY" JOURNAL OF GENERAL VIROLOGY, vol. 75, 1994, pages 1451-1456, XP002132667 page 1454, right-hand column, paragraph 2 -page 1455, left-hand column, paragraph 3	1-16

INTERNATIONAL SEARCH REPORT

Information patent family members

International Application No
PCT 00/05202

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9717084 A	15-05-1997	DE 19541284 A	30-05-1996
		CA 2236888 A	15-05-1997
		EP 0859628 A	26-08-1998
		JP 2000500124 T	11-01-2000
WO 9813378 A	02-04-1998	EP 0849275 A	24-06-1998
		AU 4401997 A	17-04-1998
WO 9701760 A	16-01-1997	FR 2736197 A	03-01-1997
		EP 0847528 A	17-06-1998